174. **(New)** The method of claim 102 wherein the known receptor is a thyroid stimulating hormone receptor.

175. **(New)** The method of claim 174 wherein the known thyroid stimulating hormone receptor has an amino acid sequence selected from the group consisting of SEQ ID NO: 395, 399, 403, 407, 411, 415, 419, and 423

a2 cont.

176. **(New)** The method of claim 102 wherein the known receptor is a Vasoactive Intestinal Peptide receptor.

177. **(New)** The method of claim 176 wherein the known Vasoactive Intestinal Peptide receptor has an amino acid sequence selected from the group consisting of SEQ ID NOS:579 and 581.

REMARKS

Claims 1-102, all the pending claims, are subject to a restriction requirement[1]. Pursuant to a telephone conference with the Examiner held on February 28, 2002, claims 1-100 have been cancelled, and new claims 103-177 have been added. Support for the new claims can be found throughout the application, especially in the claims as originally filed and in Table B, pages 12-14, and Table G, pages 65-68. No new matter has been added.

New claims 103-177 present the subject matter of claims 1-100 in an alternative format. Specifically, the claims recite a generic method (claim 103) for directly identifying a non-endogenous compound as a compound having an activity selected from the group consisting of: inverse agonists, parallel agonists, and partial agonists, to a non-endogenous, constitutively activated version of known G protein-coupled receptor, said receptor comprising a transmembrane-6 region and an intracellular region, and also recite several claims directed to application of the method to specific receptors, or families

[1] Applicants note that although only claim 102 was identified as pending in the Office Action, claims 1-102 are pending. Applicants' response to the Restriction Requirement is based on the assumption that the Restriction Requirement applies to claims 1-102.

thereof. Applicants note that claim 103 is a generic claim and, as such, is ***not*** subject to a restriction requirement.

Restriction Requirement

The Office Action has required Applicants to elect one of ninety-nine allegedly patentably distinct inventions for examination. Specifically, the Examiner alleges that "each individual sequence represents a structural and functionally distinct entity that is capable of supporting a separate patent and each method therefore requires a different composition search. The search and consideration of more than a single sequence constitutes an undue search burden on the office, given the ever-increasing size of the database." Applicants disagree and respectfully traverse the restriction requirement.

Because the Office Action has required Applicants to provisionally elect a species, Applicants elect herein SEQ ID NO:449, the amino acid sequence of mutated GPCR 5HT-6 (see page 66 of the application as filed) with traverse. Claims corresponding to the election of mutated GPCR 5HT-6 include claims new claims 103-105 (the election corresponds to canceled claims 1, 14, 101 and 102).

Applicants disagree with the imposition of the Restriction Requirement, and request its reconsideration in view of the new claims, and the remarks herein.

In accordance with the methods of the present invention, non-endogenous compounds are identified as an inverse agonist, a parallel agonist, or a partial agonist, to a non-endogenous, constitutively activated version of known G protein-coupled receptor. The steps of the invention comprise selecting a non-endogenous version of a known GPCR, confirming that the GPCR is constitutively active, contacting the candidate compound with the constitutively activated GPCR and determining whether the candidate compound has activity against the GPCR. The present specification states that the methods are broadly applicable to many known receptors, and provides exemplification of a significant number of the same.

By imposing the present restriction requirement, which appears to be based on the assertion that the application of the claimed method to each receptor is a separate invention, the Patent Office in effect asserts that Applicants are not entitled to a claim that recites Applicants' method as applied to any known receptor, but rather that

Applicants can only pursue claims applying the method to a single receptor. Thus, the Office would have Applicants file separate applications directed to the method as applied to each of the myriad known receptors for which Applicants' claimed method can be used. Such a result effectively denies Applicants meaningful protection for their invention to which they are entitled under the patent laws.

The purposes of restriction practice are to ensure that multiple patentably distinct inventions are not claimed in a single application, and to eliminate undue burdens on the Examiner arising from the same. However, restriction is not proper when it is employed to require the filing and prosecution of multiple applications directed to applications of the method to individual receptors, ***where the receptors themselves are not claimed.***

At best, the method recited in generic claim 1 could be subject to an election of species, wherein the generic claim (*i.e.*, new claim 103) would be allowed in the absence of prior art precluding allowance of a claim to a species.

It is well settled that for an application to be properly required to be restricted, there must be a serious burden on the Examiner (*see*, MPEP§803). Indeed, the MPEP states that if the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions. MPEP 803.04 states that, "It has been determined that normally ten sequences constitute a reasonable number for examination purposes." In view of this position taken by the PTO, Applicants respectfully submit that it would cause no serious burden to the Examiner to search more than one of the sequences recited in the pending claims. Moreover, Applicants again point out that any of a wide variety of known GPCRs can be used in Applicants' method, and that the invention is not confined to any single application thereof. The subject of the search, therefore, should correctly be the ***method***, and ***not*** the amino acid sequences of the various receptors for which the method can be employed.

Applicants respectfully request the reconsideration and withdrawal of the pending Restriction Requirement.

Applicants reserve the right to prosecute the claims encompassed by any of the non-elected groups in future continuing and/or divisional applications.

Attached hereto is a marked-up version of the changes made to the application by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

The examination of these claims and passage to allowance are respectfully requested. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 564-8338 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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Date: February 28, 2002

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Attachments: "Version with markings to show changes made"

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please cancel claims 1-100 without prejudice.

Please amend claim 101 as follows:

101. **(Amended)** The method of claim [1] 103 further comprising the following step:

assessing, by using an endogenous ligand based assay, the impact of the non-endogenous compound of step (d) on the binding of an endogenous ligand for the known GPCR version of the non-endogenous version of said known GPCR of step (a) with said known GPCR.